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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,954	06/25/2001	Hubert Jan Jozef Loozen	O/98414-US	9900

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EXAMINER	
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ART UNIT	PAPER NUMBER
1617	17

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/831,954	Applicant(s) LOOZEN ET AL.	
	Examiner Shaojia A. Jiang	Art Unit 1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5 and 7-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5 and 7-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 27, 2003 has been entered in Paper No. 15.

This Office Action is a response to Applicant's request for continued examination (RCE) filed January 27, 2003 has been entered in Paper No. 15, and amendment and response to the Final Office Action (mailed August 27, 2002), filed January 27, 2003 in Paper No. 16 wherein claims 2 has been amended, and claims 8-12 are newly submitted. Currently, claims 1-5 and 7-12 are pending in this application.

Claims 1-5 and 7-12 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 2 and 10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 and 10 recites the limitation "R_{11} is selected from the following group of side-chain structures" in the claim. There is insufficient antecedent basis for this limitation in the claim since the independent claims 1 and 9 define "R_{11} having a length of from 5 to 9 carbons as the longest chain on carbon atom no. 11". Thus, one of ordinary skill in the art would interpret the metes and bounds in the claims 1 and 9 as to R_{11} having a length of from 5 to 9 carbons as the longest chain on carbon atom no. 11. Therefore, the dependent claims 2 and 10 reciting the limitation "R_{11} is selected from the following group of side-chain structures" herein wherein n is an integer of from 0-9, are insufficient antecedent basis for this limitation in the claim by having more than 9 carbons on 11.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5 and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lobaccaro et al. (of record in the previous Office Action).

Lobaccaro et al. teach the active compounds, 11β-n-alkyl estradiol having ethyl, butyl, or decyl as R_{11}, which are homologs of the instant compounds, and their compositions. Lobaccaro also teaches that these compounds having R_{11} ethyl, butyl, or decyl, are known estrogenic compounds and also show antiestrogenic activity, and their

compositions. See abstract, Scheme 1 compound 5b on page 2218, Table 1 on page 2219, Table 2 on page 2221, and the 4th paragraph of page 2224. Lobaccaro et al. further teaches that the substituent at the 11β-position increase and improve the binding affinity for the estrogen receptor (ER), and that the length of the11β-n-alky arm affects the binding affinity for the estrogen receptor and these compounds show ER agonist activity and ER antagonist ERα agonist activity (see page 2219 the right column to page 2221, Table 2).

Lobaccaro does not expressly disclose the particular 11β-n-alkyl estradiol herein having a length of from 5-9 carbon atoms, and the employment of these estradiol in a method for treating estrogen deficiency disorders and a method of inducing ERα agonist activity and ERβ antagonist activity in a patient in need thereof.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular 11β-n-alkyl estradiol herein method for treating estrogen deficiency disorders and a method of inducing ERα agonist activity and ERβ antagonist activity in a patient in need thereof.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular 11β-n-alkyl estradiol having a length of from 5-9 carbon atoms in a method for treating estrogen deficiency disorders and a method of inducing ERα agonist activity and ERβ antagonist activity in a patient in need thereof, since the estradiols of Lobaccaro having 2, 4, and 10 carbons at 11β-position are known estrogenic compounds and also show antiestrogenic activity, and thus one ordinary skill in the art would have expected the estradiol compounds of Lobaccaro to

be useful in the method for treating estrogen deficiency disorders since estradiol compounds are well known to be useful the method for treating estrogen deficiency disorders.

Moreover, the substituent at the 11β-position in the compounds of Lobaccaro is known to increase and improve the binding affinity for the estrogen receptor according to Lobaccaro et al. Estrogen receptor affinity is known to discriminate two estrogen receptors, ERα and ERβ. Further, the compounds of Lobaccaro et al. show ER agonist activity and ER antagonist activity. Therefore, one ordinary skill in the art would reasonably have expected the estradiol compounds of Lobaccaro to be useful a method of inducing ERα agonist activity and ERβ antagonist activity in a patient.

The structure of the instant compounds having a length of from 5-9 carbon atoms in R_{11}, is substantially similar to the structures of their homologs having ethyl, butyl, or decyl as R_{11} in Lobaccaro. Moreover, the substituent at the 11β-position is known to increase and improve the binding affinity for the estrogen receptor, and the length of the11β-n-alky arm affects the binding affinity for the estrogen receptor to have ER agonist activity and ER antagonist ERα agonist activity. Therefore, one of ordinary skill in the art would have reasonably expected that the compounds of Lobaccaro modified from having the length of 2, 4, and 10 carbons at 11 to the length of 5-9 carbons at 11 would have possess the same or similar activity as their homologs because of the substantially close structural relationship. It has been settled that the addition of CH_3 or several CH_2 groups to a known compound is not ordinarily patentable and prima facie obvious. See *In re Wood*, 199 USPQ 137. Further, Lobaccaro has clearly provided the

motivation to the structure modification herein since he teaches that the substituent at the 11β-position increase and improve the binding affinity for the estrogen receptor, and the length of the11β-n-alky arm affects the binding affinity for the estrogen receptor , and also affects ER agonist activity and ER antagonist activity.

Thus, one of ordinary skill in the art would have reasonably expected that the instant compounds would be useful in the method for treating estrogen deficiency disorders and the method of inducing ERα agonist activity and ERβ antagonist activity in a patient.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Claims 1-5 and 7-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Napolitano et al. (of record in the previous Office Action).

Napolitano et al. teaches the active compounds, 11β-substituted estradiol derivatives having R_{11} with less than 5 carbon atoms, which are homologs of the instant compounds, and their compositions. Napolitano et al. teaches that 11β-substituted estradiol derivatives therein are known estrogenic compounds as the estrogen receptors. See abstract and Table 1 on page 2776. Napolitano et al. also teaches that the compounds having 11β-substituted show high affinity for estrogen receptor (see particularly at "Introduction" page 2774).

Napolitano et al. does not expressly disclose the particular 11β-substituted estradiol herein having a length of from 5-9 carbon atoms, and the employment of these

estradiol in a method for treating estrogen deficiency disorders and a method of inducing ERα agonist activity and ERβ antagonist activity in a patient in need thereof.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the particular 11β-substituted estradiol herein in a method for treating estrogen deficiency disorders and a method of inducing ERα agonist activity and ERβ antagonist activity in a patient in need thereof.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the particular 11β-substituted herein in a pharmaceutical composition and method for treating estrogen deficiency disorders since the estradiols of Napolitano are known estrogenic compounds and estradiol compounds are well known to be useful the method for treating estrogen deficiency disorders.

Moreover, the substituent at the 11β-position in the compounds of Napolitano is known to have high binding affinity for the estrogen receptor according to Napolitano. Estrogen receptor affinity is known to discriminate two estrogen receptors, ERα and ERβ. Therefore, one ordinary skill in the art would also have expected the estradiol compounds of Napolitano to be useful a method of inducing ERα agonist activity and ERβ antagonist activity in a patient.

The structure of the instant compounds having a length of from 5-9 carbon atoms in R_{11}, is substantially similar to the structures of their homologs having about 5 carbons or less as R_{11} in Napolitano. Therefore, one of ordinary skill in the art would have reasonably expected that the instant compounds would have possess the similar activity as their homologs because of the substantially close structural relationship. It has been

settled that the addition of CH_3 or several CH_2 groups to a known compound is not ordinarily patentable and prima facie obvious. See *In re Wood*, 199 USPQ 137. Thus, one of ordinary skill in the art would have reasonably expected that the instant compounds would be useful in the method for treating estrogen deficiency disorders and a method of inducing ERα agonist activity and ERβ antagonist activity in a patient. Further, Napolitano is seen to provide the motivation to the structure modification herein since he teaches that the compounds having 11β-substituted show high affinity for estrogen receptor.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks filed on January 27, 2003 in Paper No. 16 with respect to the rejections made under 35 U.S.C. 103(a) of record stated in the Office Action dated August 27, 2002 have been fully considered but are not deemed persuasive as to the nonobviousness of the claimed invention over the prior art. These remarks are believed to be adequately addressed by the obvious rejections presented above.

As discussed in the previous Office Action August 27, 2002 Applicant's results shown in Table A of the specification at pages 14 herein have been fully considered with respect to the nonobviousness and/or unexpected results of the claimed invention over the prior art but are not deemed persuasive for the reasons below. Table A is not seen to provide no clear and convincing evidence of nonobviousness or unexpected results over the cited prior art since Table A provides no data in support of the

conclusion that these compounds are agonist or antagonist to ER-α or EP-β. Thus, the results in Table A is considered insufficient to establish any unexpected results.

In view of the foregoing, the evidence presented in specification herein is not seen to support the nonobviousness of the instant claimed invention over the prior art.

For the above stated reasons, said claims are properly rejected under 35 U.S.C. 103(a). Therefore, said rejections are adhered to.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (703) 305-1008. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (703) 305-1877. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 305-1235.

S. Anna Jiang, Ph.D.
Patent Examiner, AU 1617
April 2, 2003